

American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility

Adopted on March 1, 2003, by the American Society of Clinical Oncology

Executive Summary: As the leading organization representing cancer specialists involved in patient care and clinical research, the American Society of Clinical Oncology (ASCO) reaffirms its commitment to integrating cancer risk assessment and management, including molecular analysis of cancer predisposition genes, into the practice of oncology and preventive medicine. The primary goal of this effort is to foster expanded access to, and continued advances in, medical care provided to patients and families affected by hereditary cancer syndromes. The 1996 ASCO Statement on Genetic Testing for Cancer Susceptibility set forth specific recommendations relating to clinical practice, research needs, educational opportunities, requirement for informed consent, indications for genetic testing, regulation of laboratories, and protection from discrimination, as well as access to and reimbursement for cancer genetics services. In updating this Statement, ASCO endorses the following principles:

- **Indications for Genetic Testing:** ASCO recommends that genetic testing be offered when 1) the individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the test can be adequately interpreted, and 3) the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer. ASCO recommends that genetic testing only be done in the setting of pre- and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities.

- **Special Issues in Testing Children for Cancer Susceptibility:** ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies and the probability of developing a malignancy during childhood. Where risk-reduction strategies are available or cancer predominantly develops in childhood, ASCO believes that the scope of parental authority encompasses the right to decide for or against testing. In the absence of increased risk of a childhood malignancy, ASCO recommends delaying genetic testing until an individual is of sufficient age to make an informed decision regarding such tests. As in other areas of pediatric care, the clinical cancer genetics professional should be an advocate for the best interests of the child.

- **Counseling About Medical Management After Testing:** ASCO recommends that oncologists include in pre- and post-test counseling the discussion of possible risks and benefits of cancer early-detection and prevention modalities, some of which have presumed but unproven efficacy for individuals at increased hereditary risk of cancer.

- **Regulation of Genetic Testing:** ASCO recommends strengthening regulatory oversight of laboratories that provide clinical cancer predisposition tests. These quality assurance mechanisms should include oversight of the reagents used in genetic testing, interlaboratory comparisons of reference samples, standardization of laboratory genetic test reports, and proficiency testing.

- **Protection From Insurance and Employment Discrimination:** ASCO supports establishing a federal law to prohibit discrimination by health insurance providers and employers on the basis of an individual's inherited susceptibility to cancer. Protections against genetic discrimination should apply to those with group coverage, those with individual health insurance policies, and the uninsured.

- **Coverage of Services:** ASCO supports efforts to ensure that all individuals at significantly increased risk of hereditary cancer have access to appropriate genetic counseling, testing, screening, surveillance, and all related medical and surgical interventions, which should be covered without penalty by public and private third-party payers.

- **Confidentiality and Communication of Familial Risk:** ASCO recommends that providers make concerted efforts to protect the confidentiality of genetic information. However, they should remind patients of the importance of communicating test results to family members, as part of pretest counseling and informed consent discussions. ASCO believes that the cancer care provider's obligations (if any) to at-risk relatives are best fulfilled by communication of familial risk to the person undergoing testing, emphasizing the importance of sharing this information with family members so that they may also benefit.

- **Educational Opportunities in Genetics:** ASCO is committed to continuing to provide educational opportunities for physicians and other health care providers regarding the methods of cancer risk assessment, the clinical characteristics of hereditary cancer susceptibility syndromes, and the range of issues related to genetic testing, including pre- and post-test genetic counseling, and risk management, so that health professionals may responsibly integrate the care of persons at increased genetic risk of cancer into the practice of clinical and preventive oncology.

- **Special Issues Relating to Genetic Research on Human Tissues:** ASCO recommends that all researchers proposing to use or store human biologic specimens for genetic studies should consult either the responsible institutional review

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Address reprint requests to Suanna S. Bruinooge, American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 1900 Duke Street, Suite 200, Alexandria, VA, 22314; email: bruinoos@asco.org.

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board (IRB) or a comparable body specifically constituted to assess human tissue research, to determine the requirements for protection specific to the study under consideration. This consultation should take place before the project is initiated. The determination of the need for informed consent or authorization in such studies should depend on whether the research involves tests for genetic markers of known clinical significance and whether research data will be linked to protected health information, as well as other considerations specific to the study proposed. Special attention should also be

paid to 1) whether future research findings will be disclosed to the research participants, 2) whether future contact of participants is planned, 3) whether and how protected health information about the tissue donors will be stored, and what will happen to study specimens after the trial ends. In addition, ASCO affirms the right of people contributing tissue to a databank to rescind their permission, in accordance with federal privacy regulations.

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IN 1996, THE American Society of Clinical Oncology (ASCO), a national medical specialty society representing cancer specialists involved in patient care and clinical research, recognized the need for greater education and awareness of the role of inherited genetic predisposition to cancer in the practice of oncology and preventive medicine. The 1996 ASCO Statement on Genetic Testing for Cancer Susceptibility¹ set forth specific recommendations relating to clinical practice, research needs, educational opportunities, requirement for informed consent, indications for genetic testing, regulation of laboratories, and protection from discrimination, as well as access to and reimbursement for cancer genetics. In 2002, ASCO's Cancer Education Committee charged its Subcommittee on Cancer Genetic Testing, with liaison membership from the Public Issues Committee, to update the 1996 Statement, taking into account advances in the field as well as interval changes in regulations and public policies. ASCO adopts this revised policy statement in an ongoing effort to continue to foster expanded access to, and continued advances in, care provided to patients and families affected by hereditary cancer syndromes.

Significant accomplishments have taken place in many of the priority areas identified in the 1996 ASCO policy statement. In the area of education, ASCO's commitment has been demonstrated by (1) publication of a resource document for curriculum development in cancer genetics education;² (2) creation of the ASCO Curriculum *Cancer Genetics and Cancer Predisposition Testing*,³ including a set of educational 35 mm slides and a CD-ROM; (3) conducting "train the trainer" educational workshops intended to expand the pool of oncologists who are equipped to teach the fundamentals of clinical cancer genetics; (4) creation of a set of clinical cancer genetics self-study materials, known as *ONCOSEP: Genetics*;⁴ and (5) conducting a series of 1-day educational symposia and 2-day comprehensive cancer genetics review courses, before the annual ASCO meeting, designed to provide both a basic core and a more advanced level of genetic information to cancer care providers and allied health care practitioners. As of 2002, these educational programs and publications have been attended or used by over 4,000 cancer care physicians and allied health professionals.

In the regulatory and policy areas, ASCO's 1996 policy statement has been cited in over 50 editorials and scholarly publications and has also been cited as part of deliberations regarding appropriateness of insurance coverage for genetic testing and counseling of individuals at hereditary risk of cancer. At the Federal level, authors of the ASCO policy statement were

invited to play an advisory role during initial planning for the National Cancer Institute (NCI)-sponsored Cancer Genetics Network and served on panels conducted by the Secretary's Advisory Committee on Genetic Testing.

Because of continued clinical and basic research advances in clinical cancer genetics, this update revisits and makes new recommendations in the following areas: indications for genetic testing, regulation of testing, insurance reimbursement, protection from discrimination, confidentiality issues associated with genetic testing, continuing educational challenges, and special research issues surrounding genetic testing of human tissues.

Indications for Genetic Testing for Cancer Susceptibility

ASCO recommends that genetic counseling and testing be offered when the 1) individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the genetic test can be adequately interpreted, and 3) the test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer. ASCO recommends that genetic testing only be done in the setting of pre- and post-test counseling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities.

None of the cancer susceptibility tests currently available is as yet appropriate for screening of asymptomatic individuals in the general population. However, in the setting of clinically defined cancer susceptibility syndromes or suggestive individual cancer histories with or without family history information, the identification of a mutation in an affected member of the family may influence medical management and can be used as a critical baseline in the testing of other family members.

Given the known limitations and wide variations inherent in models for estimating mutation probability in a given family or individual, and the lack of such models for many cancer predisposition syndromes, it is neither feasible nor practical to set numerical thresholds for recommending genetic risk assessment services. ASCO therefore recommends that evaluation by a health care professional experienced in cancer genetics should be relied on in making interpretations of pedigree information and determinations of the appropriateness of genetic testing, including determinations of appropriateness for reimbursement.

ASCO recommends that practitioners recognize indications for genetic cancer predisposition testing, where testing is part of established or evolving standards of care for risk assessment and management. In general, this includes families with features of

well-defined hereditary syndromes and individuals with very early onset disease or specific rare tumors suggestive of possible genetic hereditary predisposition. In many cases, testing information may be helpful or necessary to clarify a diagnosis. Carrier states may have different implications for dominant versus recessive syndromes.

Genetic testing for cancer susceptibility is a continually evolving field based on intense research efforts. In both common and less common familial cancer syndromes, genetic testing is playing an increasingly critical role in the medical and surgical management of identified mutation carriers and their families. Although the list of genes known to be responsible for cancer susceptibility syndromes and the medical options available to the affected individuals continues to grow, the dynamic nature of the field highlights the importance of pursuing genetic testing only in the context of pre- and posttest genetic counseling. As an educational resource, ASCO's Subcommittee on Cancer Genetic Testing has made available a table listing examples of cancer predisposition syndromes and associated genes, organized by tumor site. This table is available to oncologists and the public on the Web site describing ASCO's cancer genetics curriculum (www.asco.org) and will be updated periodically.

For many cancer predisposition syndromes, genetic testing is available through commercial laboratories (see Regulation of Genetic Testing). Before testing is performed, the clinician should provide or make available to the patient adequate genetic education and counseling in the context of that testing. Though mutations may be clearly associated with the disease or syndrome in many cases, the impact of mutation detection on medical management of carriers may be uncertain (eg, *TP53*), because of the complexity of the phenotype or the lack of effective screening or risk-reducing measures for the specific cancers involved.

In general, a definitive genetic test result may have considerable medical and psychological significance. A negative test in a family with a known deleterious mutation may provide significant emotional relief regarding personal cancer risk and risk to offspring and may result in avoidance of unnecessary medical or surgical interventions. A positive test may lead to earlier or more frequent surveillance and consideration of prevention options and may influence disease management.

Despite these benefits, genetic testing also may pose several risks. A positive genetic test and subsequent interventions may cause the patient or family to experience distress. A negative test in the absence of a known mutation in the gene analyzed may result in undue reassurance for an individual at markedly increased cancer risk by virtue of family history. The significance of an ambiguous test result (or variant of unknown significance) may be misinterpreted, with potential for adverse consequences.

ASCO reaffirms its commitment to full informed consent as part of the process of cancer genetic counseling (see Table 1). Oncologists should consider offering genetic testing only if they are able to provide or make available adequate genetic education and counseling as well as access to preventive and surveillance

Table 1. Basic Elements of Informed Consent for Cancer Susceptibility Testing

1. Information on the specific test being performed
2. Implications of a positive and negative result
3. Possibility that the test will not be informative
4. Options for risk estimation without genetic testing
5. Risk of passing a mutation to children
6. Technical accuracy of the test
7. Fees involved in testing and counseling
8. Psychological implications of tests results (benefits and risks)
9. Risks of insurance or employer discrimination
10. Confidentiality issues
11. Options and limitations of medical surveillance and strategies for prevention following testing
12. Importance of sharing genetic test results with at-risk relatives so that they may benefit from this information

options. Otherwise, they should consider referring the patient and family for these services.

Commercial availability of a new genetic test does not by itself ensure that the test is indicated for clinical application. Even in settings in which the results of genetic testing are most likely to be of clinical value, cancer specialists are strongly encouraged to offer family members participation in long-term outcomes research, to facilitate such participation, and to utilize commercial or university-based laboratories complying with federal CLIA (Clinical Laboratory Improvement Act) guidelines and committed to the validation of test results (see Regulation of Genetic Testing). Long-term outcomes studies are necessary to confirm predicted age-specific risks (penetrance) of mutations and to document the effectiveness of risk management interventions.

There is also a rapidly growing list of low-to-moderate risk gene variants, in which the significance of the detection of a germline mutation is not clear, especially for individuals without a family history of cancer. The current pace of genomics and bioinformatics research portends the development of many more low-to-moderate risk and multi-gene risk profiles. Examples of this group include mutations identified in *CDKN2A*, *CHK2*, *ATM*, *HRAS1*, and *APC I1307K* and a growing list of polymorphisms in genes associated with DNA repair and drug or carcinogen metabolism. In addition, it can be expected that variants in these and other genes will be identified that confer a protective role (decreased cancer risk). Genetic testing for these variants, including pharmacogenetic and pharmacogenomic testing, currently is in the realm of clinical research rather than standard clinical practice and requires consideration of informed consent and approval by relevant research oversight bodies (see Special Issues Related to Research on Human Tissues).

Because of the medical, social, and legal ramifications associated with genetic test results, ASCO strongly recommends that genetic testing be done only when paired with pre- and post-test counseling. This will ensure that patients are aware of the potential implications of their test results in the context of their decision of whether to seek testing. Full discussion after testing will also ensure that patients make informed medical decisions on receipt of test results (see Counseling about Medical Management after Testing for

further discussion of post-test counseling). The ASCO genetic testing curriculum provides a model for cancer specialists to have these discussions.

Special Issues in Testing Children for Cancer Susceptibility

ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies and the probability of developing a malignancy during childhood. Where risk-reduction strategies are available or cancer predominantly develops in childhood, ASCO believes that the scope of parental authority encompasses the right to decide for or against testing. In the absence of increased risk of a childhood malignancy, ASCO recommends delaying genetic testing until an individual is of sufficient age to make an informed decision regarding such tests. As in other areas of pediatric care, the clinical cancer genetics professional should be an advocate for the best interests of the child.

Genetic testing of children for cancer susceptibility raises additional challenging concerns, a full discussion of which is beyond the scope of this statement. First, except among some older adolescents, the decision to test a child is made by a parent or other surrogate rather than by the patient. Second, many adults who may have cancer predisposition syndromes decline testing. Third, testing during childhood would preclude such individuals from later deciding against being tested. Fourth, parents and healthcare professionals who decide to test a minor must consider whether and how the information will be shared with the child when she or he is older. The interested reader is referred to position papers by other organizations and commentators for comprehensive reviews of these and other questions.⁵⁻⁸

Despite the complexity of these issues, it is important to provide guidance for clinicians. ASCO recommends that the decision to offer testing to potentially affected children should take into account the availability of evidence-based risk-reduction strategies and the probability of developing a malignancy during childhood. First, when screening or preventive strategies during childhood are available (eg, MEN, FAP), testing should be encouraged on clinical grounds. Second, when no risk-reduction strategies are available and the probability of developing a malignancy during childhood is very low (eg, HBOC), testing should not be offered. Finally, some patients may be at risk of developing a malignancy during childhood without the availability of validated risk-reduction strategies (eg, TP53). The decision to test in such circumstances is particularly controversial. ASCO believes that the scope of parental authority encompasses the right to decide for or against testing this group of children and that testing should therefore not be prohibited.⁸ Nevertheless, it is important to realize that many commentators oppose testing in these circumstances⁵⁻⁷ and to ensure that parents consider the strong arguments against testing before making their decisions. As in other areas of pediatric care, the clinical cancer genetics professional should be an advocate for the best interests of the child.

A child who already carries a cancer diagnosis may also be suspected of having a predisposition syndrome. Reasons to

perform genetic tests might include a better understanding of the child's diagnosis or prognosis, decisions about potential risk-reduction strategies, considerations of risk to family members, and future reproductive decision making by the child's parents. ASCO believes that, with appropriate pre- and posttest counseling, testing of such children is ethically permissible.

Several other points merit attention. First, unless the medical benefit from testing is unequivocal, decisions about testing should involve the child in accordance with his or her developing capacity for autonomous decision making.⁹ Second, when a young child undergoes testing, providers and parents should plan to share the results (whether positive or negative) with the child when he or she has sufficient cognitive and emotional maturity to understand them. The provider should convey this expectation to the parents during pretest counseling. Reasons for disclosing this information as the child approaches adulthood include medical and reproductive decision making, the possibility that the patient may wish to communicate risk information to other family members, and the patient's need to inform his or her future healthcare providers. Discussions with the patient about test results should take place no later than the age of legal majority in the relevant jurisdiction, though in many cases it may be appropriate to share the results sooner. Because disclosure of the results of a prior test to an adolescent or young adult raises the same need for posttest counseling as initial disclosure to an adult patient, even if the test was obtained years earlier, a professional with expertise in clinical cancer genetics should participate in these discussions.

Counseling about Medical Management After Testing

ASCO recommends that oncologists include in pre- and post-test counseling discussion of possible risks and benefits of cancer early detection and prevention modalities, some of which have presumed but unproven efficacy for individuals at increased hereditary risk of cancer.

Building on the discussion necessary for informed consent, clinical oncologists should be prepared to offer family members individualized options for cancer screening, using radiographic, biochemical, endoscopic, or direct physical examination. Counseling should also include discussion of appropriate treatment options, including risk-reducing surgery (eg, mastectomy, oophorectomy, colectomy, thyroidectomy) and chemopreventive strategies, in individuals with a known mutation of a cancer predisposition gene. Although risk-reducing surgery is an accepted part of the management of some cancer predisposition syndromes (eg, FAP, MEN 2A), discussion of these options should be highly individualized in other syndromes (eg, hereditary breast/ovarian cancer), wherein data on efficacy are only emerging. Long-term follow-up trials will be necessary to demonstrate efficacy in high-risk groups, and oncologists are encouraged to offer enrollment in such studies to the families they counsel (see Indications for Genetic Testing).

Similarly, emerging data have begun to address the efficacy, or lack of efficacy, of hormonal and chemoprevention strategies (eg, tamoxifen, oral contraceptives, sulindac) in families with defined cancer predisposition syndromes. ASCO endorses the

development of guidelines based on current data and expert opinion regarding the medical management of individuals found to carry cancer predisposing mutations. Discussions of these guidelines with patients, however, should also highlight the critical research needed to document the efficacy of cancer screening and prevention in carriers of mutated cancer susceptibility genes.

A concerted effort is required on the part of the clinician to ensure that the information conveyed by a particular genetic test result is properly understood by the patient. Issues of particular concern in this regard include the meaning of a negative test in a family lacking a known deleterious mutation in the gene being analyzed, the implications of detecting a mutation of uncertain significance, and the probabilistic nature of a positive test result.

Regulation of Genetic Testing

ASCO recommends strengthening regulatory oversight of laboratories that provide clinical cancer predisposition tests. These quality assurance mechanisms should include oversight of the reagents used in genetic testing, interlaboratory comparisons of reference samples, standardization of laboratory genetic test reports, and proficiency testing.

ASCO endorses efforts to ensure the highest standards for clinical genetic testing for cancer predisposition. To attain and maintain such standards, critical elements include increased regulatory oversight over reagents, assays, personnel performing the genetic test, technical quality control, and standard format reporting of test results.

Clinical research on cancer susceptibility genes often overlaps the use of these tests in clinical practice. A clinical test, therefore, may be viewed as one in which results are provided directly to the individual being tested and may, therefore, guide medical management of either the individual or family. A clinical test may be performed in the context of a clinical research study or as a routine part of clinical care. A research test may be viewed as one that is performed primarily for the purpose of answering a predetermined hypothesis-driven question. Disclosure of research results may be of value to the patient, but it must be done with attention to all the same concerns of a clinical test.

The rapid evolution of genetic testing technologies and the pace of human genomics research continues to outpace the development of quality assurance (QA) and quality control (QC) methods for molecular diagnostics. In this field, most laboratories make their own reagents and incorporate them into their own tests. In the United States, most reagents and procedures are regulated under the Clinical Laboratory Improvement Act (CLIA) 1988 regulations. As they currently apply to genetic testing, the 1988 CLIA regulations provide a minimum and insufficient level of oversight. The Centers for Disease Control and Prevention has submitted enhanced CLIA recommendations, but these are still pending review. Several states in the United States and some European Union countries, including the United Kingdom, have developed stricter controls over cancer genetic testing.

United States–based professional societies, such as the American College of Medical Genetics (ACMG) and the College of American Pathologists (CAP), have developed inspection and interlaboratory comparison programs using trained inspectors and detailed checklists of items specific to QA/QC in the molecular diagnostics laboratory. The American Board of Medical Genetics (ABMG) and the new conjoint ABMG/American Board of Pathology (ABP) subspecialty certification in Molecular Pathology certify individuals in human molecular genetic diagnostic testing. These standardized tests apply to a wide variety of human genetic conditions, including cancer susceptibility.

In addition to meeting basic minimal regulatory requirements, ASCO believes that all genetic testing laboratories should participate in some form of proficiency testing. At a minimum, laboratories should meet the highest available standards for laboratory genetics services established by their country's certifying/regulating body.

In the United States, this includes successful participation in the CAP inspection and ACMG/CAP survey program, including state licensing and credentialing of laboratory directors and staff, taking into account such credentials as those offered by the ABMG and the ABMG/ABP. ASCO supports efforts to establish specific national policies under a standing regulatory body to assure the quality of laboratories providing genetic tests. Specifically, in the United States, ASCO supports ongoing efforts to establish specific federal policies under CLIA to assure such quality.

These efforts will aid practitioners in carefully assessing a laboratory's ability to provide accurate, state-of-the-art genetic predisposition testing to at-risk individuals. Although many national regulatory bodies oversee analytic sensitivities, they seldom have purview over clinical or scientific validity of tests. ASCO supports the efforts of professional societies to develop practice standards related to cancer genetic testing. Laboratory expertise should include knowledge of the sensitivity of the method of mutation screening used to analyze each gene, and laboratories should indicate these differences in sensitivity in the reporting of the result.¹⁰

ASCO strongly supports regulatory requirements for documentation of analytic and clinical sensitivities and specificities of mutation detection techniques and proficiency testing. In some cases, proper interpretation of complex cancer genetic test results will require the input of specialists and a multidisciplinary team of experts because of the rapidly growing knowledge base in cancer genetics. Because oncologists often provide the point-of-care for families seeking genetic testing, they should be provided the best available data regarding interpretation of a cancer genetic test.¹¹

ASCO endorses standardized test reporting, which would facilitate this process. CAP and ACMG reporting guidelines include a summary of the methods employed, objective findings, and a clinical interpretation in an easy-to-interpret format. For example, when methods involve linkage analysis, an estimate of false-positive and negative rates caused by recombination events must be provided. Similarly, if automated sequencing will miss large deletions or insertions, these limitations should be stated in

the report. Further, when a laboratory uses automated methods to identify a deleterious mutation, validation should be performed for this analysis, and a statement to this effect should appear on the report. For a disease that may be caused by mutations in any one of a number of genes (genetic heterogeneity), a negative report should emphasize the uninformative nature of the result in the absence of a known familial mutation. For a test result that describes a rare or private sequence variation, reports should reflect the clinical and biologic basis for the interpretation of the sequence variation. The report should also include information on mode of inheritance, penetrance, and other relevant aspects of genotype-phenotype correlation. Genetic counseling should be recommended within the report. Where relevant, correlation of molecular genetic data with morphologic findings should be discussed.¹²

In summary, current regulatory oversight of clinical cancer genetic testing susceptibility should be strengthened for the benefit of consumers. ASCO supports efforts to require enhanced technical quality control, including interlaboratory proficiency testing, as well as procedures that enhance the ability of laboratory directors and health professionals to deliver accurate, up-to-date cancer risk information and management recommendations based on these tests.

Protection From Insurance and Employment Discrimination

ASCO supports establishing a federal law to prohibit discrimination by health insurance providers and employers on the basis of an individual's inherited susceptibility to cancer. Protections against genetic discrimination should apply to those with group coverage, those with individual health insurance policies, and the uninsured.

Genetic discrimination with regard to health insurance has been cited as a potential problem that may be encountered by individuals with an inherited predisposition to cancer. A recent review has failed to document such discrimination in a large survey,¹³ and cancer genetics practitioners have thus far not encountered genetic discrimination in counseling and testing of women at risk of ovarian cancer. Nonetheless, fear of genetic discrimination remains a public concern. ASCO has endorsed the proposition that all Americans, regardless of health status or genetic predisposition to disease, should be guaranteed access to comprehensive and affordable health insurance.¹⁴ Although Congress has passed legislation to address certain areas of discrimination by health insurance providers, important loopholes continue to exist that allow for potential genetic discrimination.

In 1996, the 104th Congress passed the Health Insurance Portability and Accountability Act (HIPAA).¹⁵ This law greatly increases protection against discrimination by health insurance providers on the basis of an individual's susceptibility to cancer for those people covered by group or employment-based health insurance. It is important to extend the law to provide these same protections to people purchasing individual health insurance policies and to people who lack access to COBRA (Consolidated Omnibus Budget Reconciliation Act) coverage after leaving employment. Additional statutory protections are necessary to ensure that insurers will not

unfairly increase health insurance costs in the group or individual markets on the basis of family history or the results of predictive genetic tests in the absence of symptoms, clinical signs, or a diagnosis of the condition. In addition, the law should ensure that insurers and employers cannot compel individuals to take a genetic test. The law should also restrict the ability of insurers and employers to disclose the results of genetic tests.

Because HIPAA does not fully define genetic information, it does not prohibit the potential use of genetic information obtained from sources other than genetic testing; for example, from family history information. As a result, documentation of a family history of cancer in a patient's medical record could potentially be used in a discriminatory fashion. It is important to establish a statutory definition of genetic information to ensure that predictive genetic information, in the absence of symptoms, clinical signs or a diagnosis of the condition, is protected.

With regard to employment discrimination, the Americans with Disabilities Act does not provide clear protections for people with genetic markers that have not yet manifested disabling conditions. Although the Equal Employment Opportunity Commission has issued guidelines for employers on the use of genetic information, the degree of protection afforded by the law has been largely untested in the courts. ASCO supports more explicit federal statutory protections to ensure that employment decisions are not made on the basis of predictive genetic tests.

State legislators have introduced more than 60 bills regarding genetic discrimination in the workplace or genetic discrimination by insurers.¹⁶ Such state initiatives, although laudatory, may not protect all individuals. Members of the House and Senate have introduced legislation, and the need for federal law has been endorsed by the current Administration. ASCO strongly supports a federal statute to prohibit genetic discrimination by all health insurance providers and employers.

Coverage of Services

ASCO supports efforts to ensure that all individuals at significantly increased risk of hereditary cancer have access to appropriate genetic counseling, testing, screening, surveillance, and all related medical and surgical interventions, which should be covered without penalty by public and private third-party payers.

Considerable progress has been made toward the universal coverage of genetic and preventive services for individuals at hereditary risk of cancer, but important gaps remain. The Medicare program does not have a national policy providing explicit coverage for genetic testing and counseling services. In the absence of a national policy, insurance companies, which administer the program under contract with the federal government, determine, largely on a case-by-case basis, whether Medicare will cover testing services in a particular geographic region. The tests are generally covered only if they are medically necessary and diagnostic in nature. Coverage can be denied for presymptomatic testing, even though such testing may lead to effective cancer prevention.

Involvement by diverse practitioners in the Medicare Carrier Advisory Committees is critical to ensure the development of Medicare policies that reflect clinical practice.¹⁷ In the

meantime, there remain significant inconsistencies between Medicare criteria and those promulgated by other third-party payers and the practice standards of academic and professional associations. For example, reimbursement criteria should reflect the higher probability of finding certain specific mutations in some groups compared to others (eg, BRCA mutations in those of Ashkenazi ancestry).

Medicaid coverage for genetic testing is determined on a state-by-state basis. There are no data available to determine which states provide Medicaid coverage of genetic testing. Federal law does not mandate coverage of genetic testing, but gives states the option of covering it. Genetic testing to determine predisposition to a disease should be covered as a preventive or screening service or a diagnostic service if such testing would be necessary to identify a medical condition.

Genetic counseling is not universally reimbursed when provided by a licensed, credentialed, and contracted health care practitioner. There is a need for further standardization of Current Procedural Terminology (CPT) and International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes for reimbursement of genetic counseling services to ensure coverage for testing, counseling, screening, surveillance, and preventive therapy for individuals at increased risk of hereditary cancer.

ASCO strongly supports inclusion of cancer genetic testing, counseling, screening, surveillance, and preventive therapy as part of services reimbursed by Medicare, Medicaid, and private insurers.

Confidentiality and Communication of Familial Risk

ASCO recommends that providers make concerted efforts to protect the confidentiality of genetic information. However, they should remind patients of the importance of communicating test results to family members, as part of pre-test counseling and informed consent discussions. ASCO believes that the cancer care provider's obligations (if any) to at-risk relatives are best fulfilled by communication of familial risk to the person undergoing testing, emphasizing the importance of sharing this information with family members so that they may also benefit.

ASCO endorses the notion that cancer care providers should protect the confidentiality of their patients' genetic information. ASCO emphasizes the importance of including discussion of the risk to family members in pre-test counseling and informed consent discussions and includes this specific provision in the Elements of Informed Consent.

In those instances in which a genetic test reveals a marker of increased risk in a family, current case law is underdeveloped and not uniform regarding a physician's "duty to warn" family members not cared for by that physician. In one decision, a state supreme court ruled that a physician's duty to warn about a cancer predisposition syndrome was satisfied by educating the patient about familial cancer risks.¹⁸ A lower court in another state held that the physician's duty to warn extended directly to at-risk biologic relatives.¹⁹

ASCO recognizes the ethical and legal dilemmas created by efforts to breach patient confidentiality to warn relatives at high risk of inherited diseases. Such a breach may also compromise

the autonomy of the patient's relatives, who may desire not to know genetic risks within the family.

ASCO believes that physicians and other health care providers should give the highest consideration to maintaining a patient's confidentiality. In addition, federal privacy regulations allow disclosure of protected health information against a patient's wishes only in cases in which it is "necessary to prevent or lessen a serious and imminent threat to the health or safety of a person or the public."²⁰ Even for those syndromes for which there is a high cancer risk and an accepted means of prevention (eg, familial adenomatous polyposis or men2a), the maximal (mendelian) probability for a relative to inherit this susceptibility is 50%. In most adult-onset cancer syndromes, the disease probability and medical benefits associated with cancer genetic testing are still being defined. Therefore, we do not believe that the federal requirements to justify a breach of confidentiality are currently met by genetic syndromes of cancer predisposition. Further, some states (eg, New York, Illinois, and Massachusetts) prohibit communication of genetic information to anyone without the permission of the person tested.

For these reasons, ASCO believes that the cancer care provider's obligations (if any) to at-risk relatives are best fulfilled by communication of familial risk to the person undergoing testing, emphasizing the importance of sharing this information with family members so that they may also benefit.

Educational Opportunities in Cancer Genetics

ASCO is committed to continuing to provide educational opportunities for physicians and other health care providers regarding the methods of cancer risk assessment, the clinical characteristics of hereditary cancer susceptibility syndromes, and the range of issues related to genetic testing, including pre- and post-test genetic counseling and risk management, so that health professionals may responsibly integrate the care of persons at increased genetic risk of cancer into the practice of clinical and preventive oncology.

In its 1996 Statement, ASCO predicted that the assessment of inherited mutations of cancer predisposition genes would have a significant effect on the practice of clinical and preventive oncology. Although the number of oncology practitioners and genetic counselors with pertinent skills has increased significantly since 1996, the number of clinical disorders with a proven significant genetic component is also growing steadily. Cancer specialists are being asked in the course of their practice to address such issues as the evaluation of persons with a family history of cancer, the recognition of defined inherited cancer syndromes, the understanding of the process of genetic risk assessment and germline mutation testing (including risks, benefits, and limitations), and the formulation of rational management strategies (including cancer surveillance, risk reduction, and tailored cancer treatment) for individuals with inherited cancer susceptibilities. At the same time, direct-to-consumer advertising is increasing public awareness of the commercial availability of certain genetic tests for cancer susceptibility.

Because the identification of a cancer-predisposed family often takes place during the care of an individual with cancer,

oncologists and other cancer care providers are well positioned to initiate cancer genetic risk assessment. Many of the management decisions surrounding the care of cancer patients with inherited cancer-predisposing mutations require a level of clinical expertise that is most likely within the purview of the oncology practitioner or a multidisciplinary team of specialists. Cancer screening and prevention for at-risk family members may be suggested by cancer-care specialists, but their implementation requires a broad effort by a spectrum of health care providers. The number of genetic counselors, physicians, nurses, and other health care providers familiar with cancer genetic testing and risk management has been increasing.

In some cases, referral of families to specialized cancer genetics centers will be required. However, in many cases, cancer genetic counseling and management may be provided by practitioners who have made a dedicated effort to acquire specialized education in this field. For these reasons, oncologists and other health care providers in varying systems of health care delivery around the world require specialized education in molecular genetics, pedigree construction and interpretation, quantitative cancer risk assessment, and cancer risk management, as well as in the psychological, ethical, and legal complexities of genetic testing. Dedicated education and experience in cancer genetic testing and risk management are required to provide high-quality individualized counseling to both affected and unaffected members of their patients' families.

Through ASCO, a series of educational courses and symposia have been provided to almost 2,000 health practitioners. Similar educational efforts should continue and should target not only oncologists, genetic counselors, medical geneticists, and nurses but also other health professionals who will be called on to provide these cancer genetic testing and risk management services. ASCO strongly supports studies to demonstrate that genetics education information is retained over time and is used and integrated by practitioners into the clinical management of patients at increased familial/genetic risk of cancer, thus affecting the care of patients and their families.

In addition to creating the educational infrastructure required to permit cancer care providers to update their knowledge base related to clinical cancer genetics, ASCO recognizes that educational needs also exist at the level of both medical school and postgraduate medical training. ASCO is committed to facilitating the creation of a core clinical cancer genetics knowledge set so that the appropriate knowledge, skills, and attitudes may be integrated more effectively into medical school curricula, fellowship training programs, and related specialty board examinations. ASCO is convinced that adding clinical genetics to the core knowledge base on which both general and specialty board candidates will be tested can only accelerate the dissemination of this new information into the larger medical community.

ASCO also recognizes that needs and expectations in the clinical translation of cancer genetics research are rapidly evolving. As the scope and complexity of clinical cancer genetics expands, it is essential for oncology practitioners to periodically update their relevant knowledge and skills. Most important, clinicians must be able to identify those patients whose clinical

cancer genetics needs require consultation with (and possible referral to) colleagues possessing a specialized level of experience and expertise in clinical cancer genetics and genetic testing.

ASCO not only affirms the importance of training oncology practitioners to become more knowledgeable with regard to clinical genetics, but it also recognizes that it is equally vital to train primary care providers, clinical geneticists, counselors, social workers, and other preventive medicine specialists to become more knowledgeable with regard to cancer genetics, screening, and preventive oncology. These efforts should occur in concert with the integration of genetics into the preventive and therapeutic practice of other surgical and medical disciplines, as articulated by the American Medical Association (AMA) and National Coalition for Health Professional Education in Genetics (NCHPEG). ASCO encourages the relevant competence-certifying organizations, such as the 24 recognized primary specialty boards of the American Board of Medical Specialties (including the American Board of Internal Medicine, the American Board of Medical Genetics, the American Board of Surgery, and other bodies), to work in concert to address the important issues related to credentialing of clinical cancer genetics practitioners.

Finally, ASCO believes that a critical goal of all these efforts is the dissemination and maintenance of a core level of clinical cancer genetics competence among preventive oncology practitioners, thereby ensuring that all cancer patients and their families have access to high-quality clinical cancer genetics services.

Special Issues Relating to Genetic Research on Human Tissues

ASCO recommends that all researchers proposing to use or store human biologic specimens for genetic studies should consult either the responsible institutional review board (IRB) or a comparable body specifically constituted to assess human tissue research, to determine the human subjects and privacy protections specific to the study under consideration. This consultation should take place before the project is initiated. The determination of the need for informed consent or authorization in such studies should depend on whether the research involves tests for genetic markers of known clinical significance and whether research data will be linked to protected health information, as well as other considerations specific to the study proposed. Special attention should also be paid to 1) whether future research findings will be disclosed to the research participants, 2) whether future contact of participants is planned, 3) whether and how protected health information about the tissue donors will be stored, and 4) what will happen to study specimens after the trial ends. In addition, ASCO affirms the right of people contributing tissue to a databank to rescind their permission, in accordance with federal privacy regulations.

Research on biologic samples that are not anonymous from the time of collection should be considered human subjects research and should be evaluated in light of the federal regulations²¹ guiding such studies. In addition, federal privacy regulations require that biologic samples that are associated with protected health information require authorization from the

donor or an authorization exception from an IRB or privacy board.²² Research involving constitutional (germline) DNA poses special concerns because of potential implications of the research results for health risks to family members. The recommendations in this section thus pertain to research involving the analysis of constitutional DNA to detect cancer susceptibility alleles or inherited genetic alterations associated with, for example, carcinogen sensitivity or altered drug metabolism.

Although ASCO supports a more stringent review process for research involving germline DNA (ie, inherited alterations), it is important to recognize that the distinction between studies assessing somatic alterations in abnormal tissue and those evaluating germline genetic variations is somewhat artifactual. The examination of certain somatic changes by either direct DNA analysis or other techniques may indicate the presence of a germline predisposition (eg, microsatellite instability, mismatch repair protein expression, gene expression profiles).²³

ASCO, in common with other organizations, believes that respect for the persons who are the sources of biologic materials for DNA research and their families necessitates recognition that these individuals have an interest in the studies that are performed on their tissues, even when the acquisition of the tissue takes place outside of the research.²⁴⁻³¹ Research on stored samples is unlikely to pose a direct physical risk to the individuals who are the sources. Nonetheless, there may be potential social risks and psychological harms associated with such research, especially if data from the study can be linked to the donors. These risks may vary widely, depending on the specific characteristic being assessed. The situation is further complicated by the potential implications for and interest of family members in the results of germline analysis and for social or cultural groups to which the source may belong.

For these reasons, ASCO recommends that all researchers proposing to use or store human biologic specimens, other than those specimens that are not linked with protected health information, should consult either the responsible IRB or a comparable body specifically constituted to assess human tissue research, to determine the requirements for human subjects protection specific to the study under consideration. This consultation should take place before the project is initiated. Each review body should establish clear guidelines regarding what types of studies may be exempt from IRB review and what studies may be eligible for an expedited review process.

The development of expedited review processes is particularly important to avoid further burdening existing research review mechanisms. In all cases, consideration must be given to whether informed consent or authorization is required from either the individuals who are the sources of the materials or their family members before the study can proceed, how specific that consent should be, and how that consent should be acquired.

Aspects of the research design that should be considered when evaluating the need for consent or authorization include:

1. Whether the research is intended or likely to reveal information about the constitutional genotype (germline) of the source;
2. Whether information regarding the germline of the source

can be linked by either the investigator or others to information that can specifically identify the source;

3. Whether information regarding the germline of the source has established implications for prognosis, treatment, or future cancer risks of either the source or that individual's family members; and

4. Whether information regarding the results of the studies will or should be disclosed to the sources or their families, either individually or collectively.

Germline genetic information that is directly or indirectly derived from research on stored tissues may have significant implications for the individuals who are the sources of those tissues, as well as for their families. It is important to recognize that those implications may not be immediately evident at the time the genotype is determined. Review bodies should consider whether information that comes to light after the study is completed regarding the implications of the source's genotype will be disclosed to the source or the source's family, who is responsible for making the determination of need for disclosure, and how that disclosure will take place.

An important component of this consideration is the stewardship of the specimens since initial collection. Disclosure of specific individual results may be problematic because the level of stewardship in large research studies cannot be the same as that in individual clinical testing, thereby increasing the risk of sample mix-up or misidentification.

In addition, to address new hypotheses regarding the importance of specific genotypes, investigators may wish to acquire additional information about the sources at some time after the completion of the original study. Specifically constituted bodies (so called "honest brokers" who are neither in direct contact with the patients nor in a collaborative relationship with the investigators) with responsibility for maintaining links between the identifying information of the sources and the results of studies performed on their biologic materials may be of use in resolving the tension between the requirement for confidentiality and the potential need for ongoing information exchange between investigators and sources and their families. Such information exchange must also be reviewed for compliance with federal privacy regulations.

CONCLUSION

Because of the rapid pace of scientific discovery as well as policy and regulatory activity in the field of cancer genetics, ASCO will periodically review and update these recommendations. The Society is committed to continuing to expand access to, and improve the quality of, preventive oncologic care, incorporating genetic assessments, for patients and families affected by hereditary cancer.

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The ASCO Working Group on Genetic Testing for Cancer Susceptibility included:

Kenneth Offit, MD, MPH, Chair (Memorial Sloan-Kettering Cancer Center, New York, NY)

Monica M. Bertagnolli, MD (Brigham & Women's Hospital, Boston, MA); Allan T. Bombard, MD (Albert Einstein College of Medicine, Oakland, CA); Steven Come, MD (Beth Israel Deaconess Medical Center, Boston, MA); Charis

Eng, MD, PhD (Ohio State University, Comprehensive Cancer Center, Columbus, OH); Judy E. Garber, MD, MPH, and Steven Joffe, MD, MPH (Dana-Farber Cancer Institute, Boston, MA); Mark H. Greene, MD, and Margaret A. Tucker, MD (National Cancer Institute, National Institutes of Health, Rockville, MD); Stephen B. Gruber, MD, PhD (University of Michigan, Ann Arbor, MI); Jose G. Guillem, MD, MPH, and Mark Robson, MD (Memorial Sloan-Kettering Cancer Center, New York, NY); Francine E. Halberg, MD (Marin Cancer Institute, Greenbrae, CA); Healthier Hampel, MS (James Cancer Hospital and Research Institute, Columbus, OH); Olufunmilayo I. Olopade, MBBS, FACP (University of Chicago Medical Center, Chicago, IL); Paula T. Rieger, RN, MSN, FAAN (American Society of Clinical Oncology, Alexandria, VA); Miguel A. Rodriguez-Bigas, MD (M.D. Anderson Cancer Center, Houston, TX); Gail Tomlinson, MD, PhD (University of Texas Southwestern Medical Center, Dallas, TX); Michael S. Watson, PhD, FACMG (American College of Medical Genetics, Bethesda, MD); Barbara L. Weber, MD (University of Pennsylvania Cancer Center, Philadelphia, PA); Jeffrey Weitzel, MD (City of Hope National Medical Center, Duarte, CA); and Georgia L. Wiesner, MD, MS (Case Western Reserve University and University Hospitals of Cleveland, Cleveland, OH)

This policy statement was reviewed and transmitted to the ASCO Board of Directors by ASCO's Public Issues Committee, which included:

John E. Niederhuber, MD, Chair (University of Wisconsin Comprehensive Cancer Center Madison, WI)

Arlene A. Forastiere, MD, Past Chair (Johns Hopkins Oncology Center, Baltimore, MD); Maria Quintos Baggstrom, MD (University of North Carolina

at Chapel Hill, Chapel Hill, NC); Lodovico Balducci, MD (H. Lee Moffitt Cancer Center, Tampa, FL); Linda D. Bosserman, MD, FACP (Wilshire Oncology Medical Group, Inc, Pomona, CA); Jay L. Bosworth, MD (Long Island Radiation Therapy, Manhasset, NY); Marcia Brose, MD, PhD (Hospital of the University of Pennsylvania, Philadelphia, PA); Steven E. Come, MD, and Lowell E Schnipper, MD (Beth Israel Deaconess Medical Center, Boston, MA); Larry D. Cripe, MD (Indiana University Cancer Center, Indianapolis, IN); Michael Fisch, MD, MPH, Gabriel N. Hortobagyi, MD, and Leonard A. Zwelling, MD, MBA (M.D. Anderson Cancer Center, Houston, TX); Dean Gesme, MD (Oncology Associates of Cedar Rapids, Cedar Rapids, IA); Michael Goldstein, MD (Brookline, MA); Bruce G. Gordon, MD (University of Nebraska Medical Center, Omaha, NE); Julie Gralow, MD (University of Washington-Seattle Cancer Care, Seattle, WA); Steven M. Grunberg, MD (University of Vermont Medical Center, Burlington, VT); V. Suzanne Klimberg, MD (University of Arkansas for Medical Sciences, Little Rock, AR); Timothy Kuzel, MD (Northwestern University Medical School, Chicago, IL); Lawrence S. Lessin, MD MACP (Washington Cancer Institute, Washington Hospital Center, Washington, DC); Richard Pazdur, MD (Food and Drug Administration, Rockville, MD); David G Pfister, MD (Memorial Sloan-Kettering Cancer Center, New York, NY); Carolyn D. Runowicz, MD (St. Luke's-Roosevelt Hospital Center, New York, NY); Lynn M. Schushter, MD (University of Pennsylvania Cancer Center, Philadelphia, PA); Ellen V. Sigal, PhD (Friends of Cancer Research, Washington, DC); Ellen Stovall (National Coalition for Cancer Survivorship, Silver Spring, MD); and John H. Ward, MD (University of Utah School of Medicine, Salt Lake City, UT).

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